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(54) PROPHYLACTIC AND THERAPEUTIC AGENT FOR DIABETES MELLITUS AND HEALTH FOOD

(57)Abstract:

PROBLEM TO BE SOLVED: To provide an antidiabetic agent exhibiting excellent inhibitory action of activity of α -glucosidase (disaccharide hydrolase), having high safety and derived from an inexpensive plant.

SOLUTION: This prophylactic and therapeutic agent for diabetes mellitus comprises powder of a plant belonging to the genus Paris of the family Liliaceae and/or the extract thereof.

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CLAIMS

[Claim(s)]

[Claim 1] The diabetic prevention and the diabetic therapy agent which consist of the powder and/or extract of the Liliaceae TSUKUBANESOU group vegetation.

[Claim 2] The prevention and the therapy agent of diabetes mellitus according to claim 1 whose TSUKUBANESOU group vegetation is Paris polyphylla Sin., Paris polyphylla Smith, or Paris tetraphylla.

[Claim 3] Health food with which it comes to add the powder and/or extract of claim 1.

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DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[Field of the Invention] This invention relates to prevention and the therapy agent of the diabetes mellitus which used the Liliaceae (Liliaceae) TSUKUBANESOU group (Paris) vegetation for the detail more, and health food about diabetic prevention and a diabetic therapy agent, and health food.

[0002]

[Description of the Prior Art] It hydrolyzes with various enzymes, and the carbohydrate which occupies 60 – 70% in eating and drinking serves as grape sugar, is absorbed from an alimentary canal, and appears as the blood sugar level. For example, it is decomposed by the amylase, and starch serves as oligosaccharides, such as a maltose, serves as grape sugar by GURUKO cytase, is absorbed, and raises the blood sugar level. Usually, if it will be in a hyperglycemia condition, an insulin will be secreted, grape sugar are consumed, and the blood sugar level falls.

[0003] However, if superfluous secretion of the insulin by the rise of the rapid blood sugar level after eating and drinking is repeated whenever it continues for a long period of time, the symptoms of diabetes mellitus will be shown and various complication will arise by continuation of a hyperglycemia condition. Moreover, the shift to the Western foods of a high calorie accompanying West-izing of a lifestyle in recent years, overeating, the lack of movement by development of motorization, etc. become a factor, and the increment in those whom diabetic possibility cannot deny, and those who are called the so-called diabetes-mellitus reserve poses a big problem.

[0004] The sulfonyl urea agent which has a promotion operation of pancreas insulin secretion as drugs used for a diabetic therapy; Control of the glyconeogenesis of a liver, and peripheral muscles, The activity of alpha-GURUKO cytase (disaccharide hydrolase) which exists in alimentary canal membrane is checked. BIGUANAIIDO system drugs; with a sthenia operation of the insulin susceptibility in fat tissue -- thiazolidine system blood sugar rise inhibitor; -- the alpha-glucosidase inhibitor which

controls generation of grape sugar from starch or cane sugar, and controls a blood sugar level rise -- [-- for example, acarbose (the Bayer make --) There is], such as trade name Glucobay and voglibose (the Takeda Chemical, Ltd. make, trade name basin), etc., and it is used as a diabetes-mellitus therapy agent for internal use. However, generally diabetes-mellitus therapy agents including an alpha-glucosidase inhibitor are synthetic compounds. Moreover, the present condition is strict management and instruction of a medical practitioner being needed in the use -- generating of a critical hepatopathy recently being reported -- and being unable to obtain and use it easily. Furthermore, although many things which advocated the anti-diabetes-mellitus effectiveness are accepted as health food, there is much what has a question in effectiveness, and most things the efficacy in a living body and effectiveness were concretely proved to be are not accepted.

[0005] It has the effectiveness which controls the rapid grape-sugar absorption from an alimentary canal under such a situation, and prevention of the diabetes mellitus of a safe and cheap natural material and development of a therapy agent are demanded. On the other hand, Paris polyphylla Sin. which makes the Liliaceae TSUKUBANESOU group vegetation ****, Paris polyphylla Smith, and Paris tetraphylla With the China **** medicine, it is positioned as a natural drug. As drug effect of Paris polyphylla Sin. Detoxication, antiussive, sthenia, strong energy, etc. are handed down, and it is taken for the purpose of the therapy of the spasm of a carbuncle, ****, scofula, the chronic tracheitis, and a child, and recovery from fatigue, or is applied externally by the therapy of the bite of nervous dermatitis, hemorrhoids, and a snake. Paris polyphylla Smith is used as a plaster and applied externally by neoplasm poisoning. Drug effect, such as painkilling, sthenia, and tumor-suppressive, is handed down, and Paris tetraphylla is taken by debility fatigue. However, it is the natural material with which most physic study-evaluations which prove such tradition drug effect scientifically are not performed, and there is no report that the operation about diabetic prevention and a diabetic therapy was accepted in these vegetation.

[0006]

[Means for Solving the Problem] In order that this invention person may avoid generating of the failure by the repeat of the hyperinsulinism secretion in the hyperglycemia condition in after eating and drinking etc. About the natural drug which makes **** the vegetation which exists in abundance in resource, and the food by which quality was stabilized by cultivation When the research on an improvement operation of the hyperglycemia condition which made the index the operation and alpha-glucosidase inhibition activity which control the grape-sugar absorption in an alimentary canal etc. is repeated, are so safe for the vegetable extractives of the Liliaceae TSUKUBANESOU group that it can be equal to long-term continuous use. And it resulted that the depressant action, alpha-glucosidase inhibitory action, and blood sugar level rise depressant action of powerful grape-sugar absorption occurred in completion of a header and this invention. That is, according to this invention, the diabetic prevention and the diabetic therapy agent which consist of the powder

and/or extract of the Liliaceae TSUKUBANESOU group vegetation are offered. Moreover, according to this invention, the health food with which it comes to add the above-mentioned powder and/or an extract is offered.

[0007]

[Embodiment of the Invention] It is not limited especially if the vegetation which can be used for prevention and the therapy agent of the diabetes mellitus of this invention belongs to the Liliaceae (Liliaceae) TSUKUBANESOU group (Paris), and Paris polyphylla Sin. (Paris polyphylla), Paris polyphylla Smith (Paris petiolata), Paris tetraphylla (Paris tetraphylla), etc. are mentioned. concrete -- Paris polyphylla Sin.:7 You [Kazue] flower (scientific name--Paris polyphylla SMITH var.chinensis FRANCH. --) Place of production (** in China) : Chiangsu, Chehiang, Fuchien Chianghsi, ****, Hupei, Sichuan, **** Paris polyphylla Sin. (Paris polyphylla SMITH var.platypetalaFRANCH. --), such as Kueichou, Yunnan, Kuangtung, and Kuanhsi Sichuan, Yunnan, and **** Paris polyphylla Sin. (Paris polyphylla SMITH var.pubessens HANDMAZZ. --) Sichuan, Yunnan, and Paris polyphylla Smith (Paris polyphylla SMITH var.stenophylla FRANCH. --) Sichuan, Yunnan, and a gold streak -- Paris polyphylla Smith (Paris polyphylla SMITH) Yunnan Paris polyphylla Smith (Paris polyphylla SMITH var.yunnanensis FRANCH. and HAND-MAZZ. --), such as Kueichou, Yunnan, Sichuan, and Tibet Yunnan and true love (Paris verticillata Paris quadrifolia L.= --) Japan, such as Shanhsi, Korea, Sakhalin, Siberia, and Paris polyphylla Smith:**** Paris tetraphylla (Paris petiolata BAK ex FORB. --) Paris tetraphylla, such as Sichuan and Kuanhsi: It is TSUKUBANESOU (Japan, such as Paris tetraphylla A.GRAY, Chiangsu, Chehiang, Chianghsi, ****, and Sichuan, Korea) etc. (based on the volume for "inside medicine great dictionary" Shogakukan above).

[0008] Although these vegetation is considered that some difference is in the amount and class of component which are contained in it by a class, the place of production, etc., what is being grown in which [besides places of production, such as China, Korea, Japan, Sakhalin, and Siberia,] area can be used for it. Such vegetation can use all the parts of TSUKUBANESOU group vegetation, such as not only the roots, such as a rhizome, but a leaf. When using as powder, the extracted vegetation can be preferably prepared as powder of 200-500 meshes 100-1000 meshes remaining as it is or by drying and grinding with a grinder etc.

[0009] Moreover, when using as an extract, with solvents, such as water, lower alcohol (a methanol, ethanol, butanol, etc.), or such mixture, the rear stirrup dried as it was can be ground, maceration of such vegetation can be heated or carried out, and it can obtain. It is appropriate to vegetation about 2-10 weight twice and to use a solvent about 2-5 weight twice preferably. Moreover, an extract can be prepared by heating at about 40-80 degrees C for about 1 to 10 hours, or carrying out grade immersion of the vegetation for one - ten days under shaking or non-shaking at the maceration temperature of about 10-35 degrees C.

[0010] The obtained extract may be condensed and used. It is desirable to perform concentration under low-temperature low voltage. Moreover, this concentration may

be performed until it hardens by drying. In addition, it may filter, before condensing, and a filtrate may be condensed. Moreover, the obtained extract may be given to purification processing. As a purification art, independent or the approach of combining and using it is mentioned in chromatography, the segregation process which uses ion exchange resin.

[0011] For example, the approach of using it as chromatography combining normal phase chromatography, reversed phase chromatography, high performance chromatography, centrifugal liquid chromatography, a column chromatography, thin-layer chromatography, or them is mentioned. Purification conditions, such as support in this case and an elution solvent, can be suitably chosen corresponding to various chromatographies. For example, in the case of normal phase chromatography, in the case of the solvent of a chloroform methanol system, and reversed phase chromatography, the solvent of a water-methanol system can be used.

[0012] Moreover, water or lower alcohol is made to dilute / dissolve the obtained extract as a segregation process which uses ion exchange resin, and after contacting this solution on ion exchange resin and making it adsorb, the approach of eluting with lower alcohol or water is mentioned. In this case, the lower alcohol used is as having mentioned above, and its methanol is desirable especially. As ion exchange resin, especially if used for purification processing of the field concerned, it is not usually limited, and the polystyrene system resin with which the bridge was constructed over porosity by huge network structure, an urban light, a cellulose, etc. are mentioned. The powder and/or extract of the Liliaceae TSUKUBANESOU group vegetation can be used with various gestalten, such as granulation, a tablet, and a capsule, by the well-known approach in the manufacture field of drugs or food with a salt [**** / in physic], an excipient, a preservative, a coloring agent, corrigent, etc.

[0013] Moreover, the powder and/or extract of the Liliaceae TSUKUBANESOU group vegetation can be used for health food. In semantics with more positive health food than the usual food, the food made into the purposes, such as health, and health maintenance, improvement, is meant, for example, confectionary, such as Cookie, a rice cracker, jelly, sweet bean paste, yogurt, and steamed filled dumplings, a soft drink, a nutrition drink, soup, etc. are mentioned to a liquid or a half-solid, a solid product, and a concrete target. Moreover, it brews as it is and is good also as species. In the production process of such food, mixing or spreading, spraying, etc. can add by carrying out to a final product, and the above-mentioned powder, an extract, etc. can be used as health food at it.

[0014] It is desirable for about 10–200mg about 10–50mg to be preferably mentioned, corresponding preferably about 50–1000mg with powder per adult to the degree of purification in about 50–300mg and an extract, a moisture content, etc., in order to use for prevention, for example, although the amount of the powder of the Liliaceae TSUKUBANESOU group vegetation and/or the extract used changes with age, symptoms, etc., and to carry out a three times a day in time-before-a-meal about 30 minutes. Moreover, at the time of the use as health food, it is appropriate to be the

gestalt of powder and an extract and to use in about 10–1000mg to 1kg of amounts which do not have a bad influence on the taste or appearance of food, for example, the target food. Below, prevention of the diabetes mellitus of this invention and the example of a therapy agent are explained in detail.

[0015] The 2–3l. solvent (water, a methanol (1% of moisture content), ethanol (5% of moisture content), butanol) was added to 1kg of rough **** of extract Paris polyphylla Sin. of the Liliaceae TSUKUBANESOU group vegetation, Paris polyphylla Smith, and Paris tetraphylla, respectively, at 80–90 degrees C, heating or maceration was carried out for three days for 3 hours, and the cooling back fault was carried out, and under reduced pressure of the filtrate, the solvent was distilled off under temperature about 45 degrees C or less, and it considered as the solid extract. In heating, the yield of water extractives was about 5 – 8% about 9 to 12% with ethanol extractives about 10 to 15% with methanol extractives about 14 to 18% at butanol extractives. Moreover, in maceration, yield was an about 20% decrease in heating. Each water extract of obtained Paris polyphylla Sin. and Paris polyphylla Smith showed strong hygroscopicity with light yellow powder. Moreover, in the thin-layer chromatography under the following conditions, the black spot was all obtained by an yellowish green spot and the 0.7 neighborhoods to the Rf value 0.8 neighborhood at the some brown spots and 0.3 neighborhood.

[0016] Support: Silica Gel 60F254 pre-coated TLC plate (product made from Merck) expansion solvent: -- chloroform: -- methanol: -- water (6:4:1)

Coloring: It is based on the coloration at the time of heating after spraying 10% sulfuric-acid water solution which contains cerium <4> sulfate 1%. Furthermore, by the ultraviolet absorption spectrum (Shimazu UV-1600, a solvent: methanol), absorption maximum was shown near 280nm and each showed sh absorption near 245nm.

[0017] In the IR spectrum (Shimazu FTIR-8100 (KBr)), the absorption considered with each to originate in a hydroxyl group and the 2940cm⁻¹ neighborhood in methylene and the 1630–1660cm⁻¹ neighborhood, and to originate in ether linkage in a carbonyl group, an olefin or an amide group, and the 1050cm⁻¹ neighborhood by the 3430cm⁻¹ neighborhood was accepted.

[0018] Preparation of the activity inhibition trial enzyme of the alpha-glucosidase: The brush border membrane obtained from the jejunum of a Wistar system male rat (weights 150–350g) was used as a crude enzyme. This brush border membrane was suspended in the 0.01M maleic-acid buffer solution (pH=6.0), and was diluted to the concentration by which the substrate for about 25 – 50 n mol/ml/is hydrolyzed. Brush border membrane was used because d-GURUKO cytases, such as a maltase and sucrase, were contained in abundance. The examining method: As a substrate, by 74mM(s), 100micro of things L of each concentration of 50microL and subject extractives (water extractives or ethanol extractives) was added, and preliminary warming of each of a maltose and sucrose was carried out for 2 – 3 minutes at 37 degrees C. In addition, both a substrate and subject extractives were dissolved and

used for the maleic-acid buffer solution (PH=6.0).

[0019] Next, 50micro of enzyme liquid L was added to this, and it was made to react to it for 30 minutes. A halt of a reaction added 800micro of water L, and was performed by putting in for 2 minutes during a 92-97-degree C water bath. The generated amount of glucoses was measured with the glucose oxidase method (glucose C11 Test Wako). In addition, as an example of a comparison, sweet taste was controlled alternatively and the amount of glucoses which obtained like the above the extractives of the Gymnema leaf known if there is an operation which delays absorption of the sugar from intestines, examined them similarly, and generated them was measured. The following results were obtained when the amount of extractives required to check alpha-glucosidase activity 50% was calculated from the obtained result. The result is shown in Table 1.

[0020]

[Table 1]

	IC ₅₀ (μg/ml)	
	ショ糖	麦芽糖
蚕休水エキス	18.7	60.0
重楼水エキス	10.2	48.0
王孫水エキス	20.1	60.5
ギムネマ葉水エキス	500以上	500以上
蚕休イタノ-ルエキス	60.3	180.5
重楼イタノ-ルエキス	42.5	120.6
王孫イタノ-ルエキス	55.7	50.0
ギムネマ葉イタノ-ルエキス	500以上	500以上

From Table 1, each of Paris polyphylla Sin., Paris polyphylla Smith, and Paris tetraphylla extractives was understood that the activity inhibitory action of the alpha-glucosidase is strong. Moreover, activity inhibition ability with the water extractives more expensive than methanol extractives was shown.

[0021] the Wister system male rat (weights 130-170g) in a cane-sugar load which carried out the blood sugar level rise depressant action fast -- using -- six groups -- ** -- it carried out and the water extractives and the powder of Paris polyphylla Sin., Paris polyphylla Smith, and Paris tetraphylla were administered orally, respectively. The load (0.5 g/kg is administered orally) of the cane sugar was carried out after the 30 minutes. It collected blood from the carotid artery under non-anesthetized constraint (at the time of blood collecting) a sugar load, 30 minutes, and 1 hour after, and the blood sugar level was measured. In addition, the blood sugar level was measured with the glucose oxidase method. In addition, powder ground desiccation rough **** of Paris polyphylla Sin., Paris polyphylla Smith, and Paris tetraphylla with the grinder, and made it about 500 meshes. Moreover, same measurement was

performed, using the extractives of the *Gymnema* leaf as an example of a comparison. The result is shown in Table 2.

[0022]

[Table 2]

	用量 (mg/kg、経口投与)	匹数	血糖値 (mg/dl)	
			30分後	1時間後
正常群	—	6	89.1 ± 3.3	94.5 ± 4.6
対照群	—	6	184.0 ± 6.4	155.0 ± 5.4
蚕休水エキス	50	6	142.6 ± 7.1	136.6 ± 4.6
	100	6	108.3 ± 3.5	122.1 ± 1.8
	200	6	95.6 ± 3.1	116.7 ± 3.3
重楼水エキス	50	6	139.3 ± 6.8	135.2 ± 4.6
	100	6	104.3 ± 3.1	120.1 ± 1.5
	200	6	94.2 ± 3.3	110.0 ± 2.4
王孫水エキス	50	6	156.2 ± 7.3	140.6 ± 5.0
	100	6	126.3 ± 4.1	129.2 ± 5.4
	200	6	101.8 ± 3.0	113.1 ± 4.3
蚕休粉末	500	6	118.6 ± 7.8	122.3 ± 6.4
重楼粉末	500	6	120.3 ± 6.7	126.2 ± 6.3
王孫粉末	500	6	125.4 ± 8.6	128.4 ± 4.8
ギンナ葉水エキス	500	6	171.6 ± 7.5	150.0 ± 5.6

From Table 2, *Paris polyphylla* Sin., *Paris polyphylla* Smith, and the *Paris tetraphylla* extractives were all understood that the blood sugar level rise depressant action in a cane-sugar load is strong in in vivo ones.

Weighing capacity of the health food example 1 wheat-flour 50 weight section which the extract of the Liliaceae TSUKUBANESOU group vegetation contained, the sugar 35 weight section, the whole egg 10 weight section, and the water extractives 5 weight section obtained by the above was carried out. After mixing sugar to a whole egg, through wheat flour was beforehand added to the screen, it mixed lightly, and the ground was made, this was fabricated in the suitable form, it roasted in oven, and the rice cracker was made.

[0023] an example 2 -- the capsule was filled up with the water extractives obtained above according to the well-known approach in the field concerned, and the gelatine capsule contained 50mg in 1 capsule was obtained.

[0024]

[Effect of the Invention] According to this invention, since alpha-glucosidase inhibitory action and the blood sugar rise depressant action at the time of a sugar load occur, the powder and/or extract of the Liliaceae TSUKUBANESOU group vegetation of this invention not only control the hyperglycemia condition after eating and drinking resulting from overeating, an unbalanced diet, etc., but it can use them effectively as a therapy agent of the diabetes mellitus which can also be said to be

the representation of a lifestyle-related disease. Moreover, since it is the natural drug which makes **** the vegetation based on a long use experience, and there are no worries about a side effect etc. and it can use cheaply, it is effective also in a diet or diabetes-mellitus prevention. And the powder and/or extract of the Liliaceae TSUKUBANESOU group vegetation of this invention being taken easily, and taking them, since it can carry out to the gestalt which is easy to take in as health food, for example, the gestalt of confectionery, a drink, etc., can be continuously continued over a long period of time.

[Translation done.]